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F-737

AUG 11 2008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Andreas SEWING et al. :

Group Art Unit: 1616

Serial No.: 09/885,287 :

Examiner: Gollamudi S

Filed: June 21, 2001:

For: COATING FOR METALLIC IMPLANT MATERIALS

BRIEF ON APPEAL

Mail Stop
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on 8 June 2008, please consider the following:

Payment is made by credit card via EFS to include the fee as set forth under § 41.20(b)(2). The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

This is an appeal from the decision of the Examiner rejecting claims 1, 3-8, 10, 12-19, 21, 23-28 of the above-identified application.

(i) REAL PARTY IN INTEREST

The present application is assigned to Biomet Deutschland GMBH, by means of an assignment recorded at reel 014797, frame 0110.

(ii) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

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(iii) STATUS OF CLAIMS

Claims 1, 3-8, 10, 12-19, 21, 23-28 are rejected.

Claims 2, 9, 11, 20 and 22 are cancelled.

Claims 1, 3-8, 10, 12--19, 21, and 23-28 are all on appeal.

(iv) STATUS OF AMENDMENTS

Appellants' amendment filed 31 October 2007, has been entered.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

The invention involves, in claim 1, a coated metallic implant comprising a metallic implant having a surface and an outer layer. The outer layer comprises a bone analogous coating having a collagen matrix mineralized with a calcium phosphate phase that is adhered to the implant surface. The mineralized collagen matrix is constructed in the form of layers, whereby at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite and the crystals of said crystalline hydroxyapatite have a length of about 300 to 500 nm. The coated metallic implant is prepared by a process comprising:

- a) coating the metallic implant material by immersion in a collagen solution at a pH of less than 8 and a temperature between 4 – 40°C, and
- b) coating the metallic implant material with a calcium phosphate phase (CCP) in a electrochemically assisted process by means of cathodic polarization in an electrolyte solution comprising calcium ions and phosphate ions. Process steps a) and b) may be performed simultaneously or sequentially.

See for example original claims 1 and 3 and the specification at page 5, lines 30-38. Also see page 7 lines 8-20.

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The invention also involves, as recited in claim 26, a coated metallic implant comprising a metallic implant and a coating made of a collagen matrix mineralized with a calcium phosphate phase. The calcium phosphate phase is doped with fluoride, silver, magnesium or carbonate ions or combinations thereof. The collagen is a mixture of collagen of types I to III. The coatings may be obtained by precipitating calcium phosphate from a solution in the presence of collagen. See, the examples, and page 8, line 20 to page 12.

The invention also involves, as recited in claim 28, a coated metallic implant comprising a metallic implant having a surface and an outer layer, wherein the outer layer comprises a bone analogous coating comprising a collagen matrix mineralized with a calcium phosphate phase which is adhered to the implant surface. The mineralized collagen matrix is constructed in the form of layers, whereby at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite, wherein the crystals of the crystalline hydroxyapatite have a length of about 300 to 500 nm. See for example, page 5, last paragraph and Example 3 on page 12 of the specification.

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1) Claims 1, 4, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in further view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441).

2) Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441) in further view Sauk et al (4,780,450).

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3) Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441) in further view of Geistlich et al (5,573,771).

4) Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by Rhee (5,543,441) in further view of Liu (6,300,315).

5) Claims 1, 3-5, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441).

6) Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441) in further view of Sauk et al (4,780,450).

7) Claims 1, 3-4, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441).

8) Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441) in view of Sauk et al (4,780,450).

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9) Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441) in further view of Geistlich et al (5,573,771).

10) Claims 1, 3-6, 8, 10, 12-16, 18-19, 23-25, 27-28 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Constantz et al (5,279,831) in view of Liu (6,300,315) optionally in further view of Lussi et al (5,167,961) and as evidenced by Rhee (US 5,543,441).

11) Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Constantz et al (5,279,831) in view of Liu (6,300,315) optionally in view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441) in further view Sauk et al (4,780,450).

12) Rejection of Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27-28 under the doctrine of obviousness-type double patenting.

(vii) ARGUMENTS

1) Claims 1, 4, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in further view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441).

On page 8 of the Office Action, the Examiner cites the Webster dictionary definition of "mineralize", despite the inventors meaning of the phrase "mineralized collagen matrix", which is clear from the intrinsic record. There is a considerable difference between the structure of a simple mixture of collagen and calcium phosphate or hydroxyapatite, respectively, and the structure of a "mineralized collagen matrix". The claimed metallic implant is coated with a

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mineralized collagen matrix that is structurally very different from a simple admixture of collagen and hydroxyapatite as disclosed or derivable from prior art.

The inventors meaning of the phrase "mineralized collagen matrix", is clear from the intrinsic record. See, *Jack Guttman v. Kopykake Enterprises, Inc.*, 302 F.3d 1352 (Fed. Cir. 2002), "It is black letter law that a patentee can "choose to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term that could differ in scope from that which would be afforded by its ordinary meaning." *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342, 60 USPQ2d 1851, 1854 (Fed. Cir. 2001)." Appellants' may be their own lexicographer and need not explicitly define a term or phrase. The first line of Appellants' specification states: " The invention relates to a biomimetically produced bone analogous coating..." As pointed out on page 3, lines 4-12 of the specification in reference to the prior art: "Methods which comprise both hydroxyapatite and collagen are only restricted to mixtures of the components....". Thus, the specification clearly teaches a skilled worker that the mineralized collagen matrix according to the invention is not a simple mixture of hydroxyapatite and collagen, like the prior art, but is instead is biomimetically produced and bone analogous.

It is clear from Appellants' specification (and the claim language) that the matrix is biomimetically produced from an electrolyte solution. See page 4 line 39-40 of the specification. Furthermore, the mineralized collagen matrix is in the form of layers. See page 5, line 15-19 and the claim language. Electron microscope examination, X-ray diffraction investigations and IR-spectroscopic investigations are used to characterize these layers. See examples 1-4. Furthermore, as seen on page 11 of the specification, the collagen is not present in denatured form. On the contrary a good agreement exists between the mineralized layer and a spectrum from native bone. Thus, the mineralized collagen matrix is constructed in the form of layers. At least one of the layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate clusters and crystalline hydroxyapatite. Crystals of hydroxyapatite having a length of about 300 to 500 nm are present on and between the collagen fibrils.

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Contrary to the Examiners assertion on page 7, line 16 of the February 2008 Office Action, Appellants' need not explicitly define a term or phrase. As stated in the MPEP at section 2111.01 (IV), the specification should also be relied on for more than just explicit lexicography or clear disavowal of claim scope to determine the meaning of a claim term when applicant acts as his or her own lexicographer; the meaning of a particular claim term may be defined by implication, that is, according to the usage of the term in the context in the specification. See Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) (en banc); and Vitronics Corp. v. Conceptronic Inc., 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1577 (Fed. Cir. 1996). Applicant's have clearly defined "mineralized collagen matrix". It has been consistently used in the context of "bone analogous coating" and in the form of layers produced biomimetically from an electrolyte solution.

In construing claim terms, the general meanings gleaned from reference sources, such as dictionaries, must always be compared against the use of the terms in context, and the intrinsic record must always be consulted to identify which of the different possible dictionary meanings is most consistent with the use of the words by the inventor. See ACTV, Inc. v. The Walt Disney Company, 346 F.3d 1082, 1092, 68 USPQ2d 1516, 1524 (Fed. Cir. 2003). Absent an express definition in the specification a term should be given its broadest reasonable interpretation consistent with the intrinsic record and take on the ordinary and customary meaning attributed to it by those of ordinary skill in the art. See E-Pass Technologies, Inc. v. 3Com Corporation, 343 F.3d 1364, 1368, 67 USPQ2d 1947, 1949 (Fed. Cir. 2003).

On page 8, line 5 of the February 2008 Office Action the Examiner cites Du et al. The Du et al. reference further supports Appellants' position that the term "mineralized collagen matrix" does not mean a simple admixture as the Examiner alleges. At page 519, Col. 1 it is stated:

"Natural bone is a complex biomineralized system with an intricate hierarchical structure.⁹ It is assembled through the orderly deposition of apatite minerals within a type I collagenous organic matrix."

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Du et al. goes on to describe the hydroxyapatite crystals that grow on the collagen fibrils. The naturally given size of a collagen fibril is about 3000 Å. As discussed on page 173 of Lehninger "Principles of Biochemistry" previously provided, collagen is a rod-shaped molecule of about 3,000 Å long (300 nm) and 15 Å thick. In order to form bone analogous structures of interconnected layers, the calcium phosphate crystallite growth has to occur on and between the collagen fibrils. Thus, in bone analogous structures the hydroxyapatite crystals must be small enough to interact within the collagen fibrils, which have a size of about 0.3 µm or 3000 Å. Hydroxyapatite crystals of a size between 2 to 20 µm (i.e., 2000-20,000 nm) are much too large to grow on and between collagen fibrils. Using hydroxyapatite crystals of a size much larger than collagen fibrils would result in domination of the mineral component, thereby creating a simple admixture of the collagen into the mineral matrix (i.e., there would be no interconnection between the crystals and collagen fibrils). Therefore, hydroxyapatite crystals formed on the fibrils cannot be excessively larger than the size of a collagen fibril, i.e. 300 to 500 nm. The size of the hydroxyapatite crystals according to the claims is between 300 to 500 nm. Due to the applied electrochemical process the crystals cannot be larger than that.

The Du et al. reference further teaches a skilled worker that mineralized collagen is a common scientific term, and it is not a simple mixture. A key step in Du's mineralization process is the growth of calcium phosphate minerals on a collagen matrix in aqueous media (page 519, left column, third paragraph). Additionally, Du et al. teaches that mineralized collagen as bone analogous material can only be obtained under precise reaction conditions. According to Du et al. the preferred approach for obtaining a mineralized collagen comprises soaking a collagen matrix in a phosphate solution with a pH of 14 (solution B) followed by immersing in a calcium chloride solution (solution A, page 520, right column, first paragraph). Under Du, a very specific step of sequences is used to provide a mineralized collagen matrix.

Appellants' note however that the membrane of Du et al. cannot be used in an electrochemical process due to a lack of electrical charges on the membrane

surface. Furthermore, the formation of calcium phosphate on the collagen fibrils and the subsequent washing removes all charged particles from the membrane (page 525, left column, second paragraph of Du et al.).

Thus, a skilled worker would recognize from Du et al. that achieving a mineralized collagen matrix requires very specific conditions. It cannot be formed from a simple admixture of hydroxyapatite and collagen.

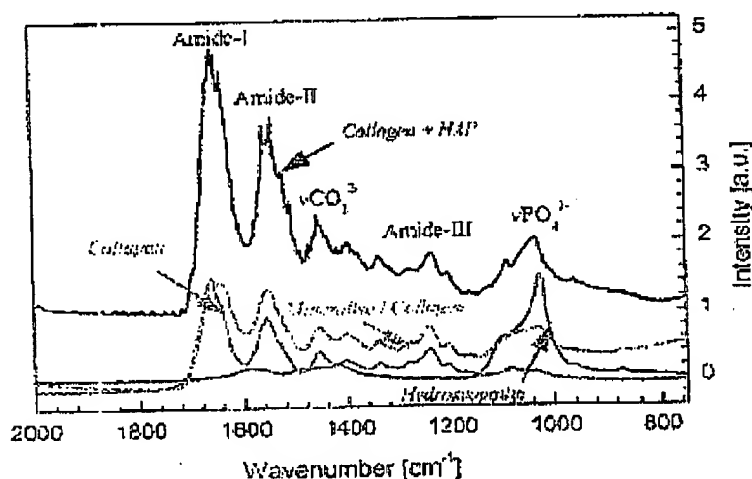
In the rejection the Examiner cites a multitude of references (JP '259, Constanz, Lui, Lussi, Rhee, Sauk, Geistlich, Worch and Shirkanzadeh) to make various obviousness rejections. However, even piecing these references together in hindsight reconstruction does not arrive at the present invention. The mineralized collagen matrix of the present invention is constructed in the form of layers, whereby at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite, wherein the crystals of said crystalline hydroxyapatite have a length of about 300 to 500 nm. This alone establishes patentability of the claimed invention. However, as noted in the first line of the specification the bone analogous coating is biomimetically produced. Thus, in the interest of furthering prosecution, in the 31 October 2007 response, Appellants' amended claim 1 to include the process of preparing the biomimetically coated implant. Thus, Appellants' have distinguished the implant of the present invention from the prior art products not only in terms of composition and/or structure but also by the unique process of making. As can be seen in related continuation application 10/414,284 (now US 7,229,545) the USPTO determined that the process of making the implant of the present invention was patentable. None of the cited prior art teaches or suggests the process of making the coating of the present invention.

On page 8 of the February 2008 Office Action, the Examiner alleges that the Appellants' have not provided evidence establishing an unobvious difference between the claimed product and prior art product. The Examiner has provided no evidence other than mere speculation, that the product of the prior art is identical to the product of the present invention. The Examiner is relying on a multitude of references and various combinations of products. It is not clear from

the record which prior art product the Examiner alleges is identical to the Appellants' claimed product. However, it is clear from the record that the claimed process features, impart a structurally defining feature to the coating of the claimed invention. Additionally, the Examples in the specification provide electron microscope examinations, X-ray diffraction investigations and IR-spectroscopic investigations to characterize the claimed invention.

To illustrate the difference between a simple admixture of collagen and hydroxyapatite, on the one hand, and mineralized collagen according to the invention, on the other hand, Appellants' previously present the following Fourier Transform Infrared (FTIR) spectra: (Figure 1).

Figure 1



This figure shows the FTIR spectra of

- collagen,
- hydroxyapatite,
- a mixture of collagen and hydroxyapatite ("Collagen + HAP") which was manufactured by mixing hydroxyapatite particles and collagen and subsequent freeze-drying according to a process similar to that described in US 5,246,457 and

d) a mineralized collagen matrix according to the invention ("mineralized Collagen").

As can be clearly seen from the FTIR spectra, especially from the position of the amide-I band (C=O stretching vibration; here around 1650 to 1660 cm^{-1}), the relative intensity between the amide-I and the amide-II band (N-H bending vibrations coupled with C-N stretching vibrations; around 1550 cm^{-1}) and the phosphate stretching vibration (between 1000 and 1150 cm^{-1}), the spectrum of the mixture of collagen and hydroxyapatite ("Collagen + HAP") represents merely an addition of the single spectra of collagen ("Collagen") and hydroxyapatite ("hydroxyapatite"). This is due to a lack of interactions of hydroxyapatite and collagen in a mixture of both compounds.

On the other hand, a mineralized collagen matrix according to the invention ("mineralized collagen") shows a markedly different spectrum than collagen ("Collagen"). The higher the grade of mineralization of the collagen matrix, the broader the amide-I band becomes. Concomitantly, the maximum of the amide-I band shifts to lower wave numbers (from about 1659 to 1656 cm^{-1}). This is generally considered to be due to a higher degree of hydrogen bonds within the material and is indicative of the changed secondary structure of the collagen matrix due to mineralization.

Another molecular structural explanation of the amide-I band shift is a decreasing electron density between the carbon and the oxygen of the C=O bond due to the incorporation of phosphate and calcium ions. Further, the more energetically different states of the C=O bonds of the mineralized collagen matrix exist, the broader the amide-I band becomes. The energetically different states also arise by interactions of collagen with positively (calcium) and negatively charged ions (phosphate) during mineralization.

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Normal non-mineralized collagen, hydroxyapatite and the mixture of both show sharp bands clearly differing from the broad amide-I band of a mineralized collagen matrix according to the invention. Further, the ratio between the intensity of the amide-I band and the intensity of the amide-II band changes significantly during the mineralization process of collagen. As is evident from Figure 1, the amide-I to amide-II ratio remains almost constant between collagen ("Collagen") and a mixture of collagen and hydroxyapatite ("Collagen + HAP"). However, the relative intensity of the amide-II band is much higher in case of a mineralized collagen matrix according to the invention. By mineralization the peptide bonds of collagen become much more prone to N-H bending vibrations and C-N stretching vibrations.

Additionally, as can be seen from Figure 2 below, the FTIR spectrum of a mineralized collagen matrix much more closely resembles the spectrum of bone than that of normal non-mineralized collagen.

Figure 2

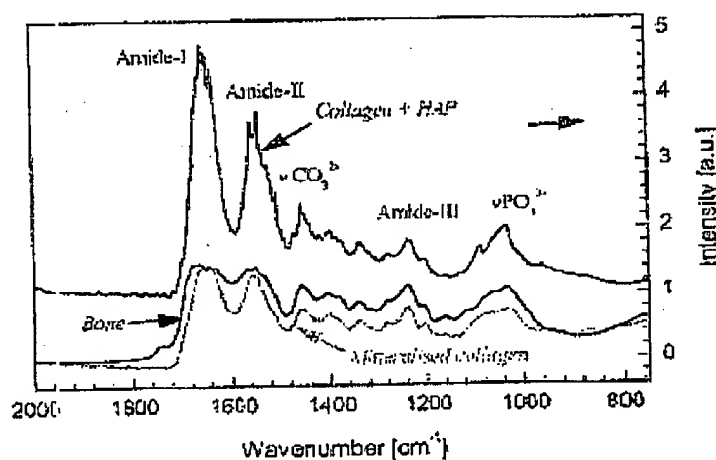


Figure 2 shows the FTIR spectra of

a) a mixture of collagen and hydroxyapatite ("Collagen + HAP") which was manufactured by mixing calcium phosphate particles and collagen and

subsequent freeze-drying according to a process similar to that described in US 5,246,457,

b) bone ("bone") and

c) a mineralized collagen matrix according to the invention ("mineralized collagen").

As can be clearly seen from the FTIR spectra of Figure 2, bone ("bone") shows a broad amide-I band having sub-maxima, a fact also known from literature. The reason for this broad amide-I band can be seen in many different states of collagen existing in bone material in parallel. These different states are detected by FTIR spectroscopy integrally.

Besides the impact of collagen molecules and fibrils in different mineralization states, it is believed that such a broad amide-I band is also due to conformational changes of the collagen by mineralization, particularly due to a smaller cross striation (changing from 67 to 64 nm).

The amide-I to amide-II intensity ratio is almost 1:1 in the case of bone material.

By comparing the spectra of bone and of a mineralized collagen matrix, it is apparent that these spectra are extremely similar. On the other hand, both the spectra of normal collagen and of a mixture of collagen and hydroxyapatite are significantly different from both the spectrum of bone and from the spectrum of mineralized collagen matrix.

Thus, the claimed metallic implant is coated with a mineralized collagen matrix that as noted above is structurally very different from a simple admixture of collagen and hydroxyapatite as disclosed or derivable from prior art. The

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claimed mineralized collagen matrix is constructed in the form of layers that comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite crystals having a length of about 300 to 500 nm.

Thus, Appellants' have shown that the process of making the coating according to the invention results in a clear physical distinction from the products of the prior art. Under such circumstances, the claimed pure compound is non-obvious. See, for example, *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968) in which the court held "the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds".

As noted above, the claimed metallic implant is coated with a mineralized collagen matrix that is structurally very different from a simple admixture of collagen and hydroxyapatite as disclosed or derivable from prior art.

JP11-047259

JP 11-047259 relates to an implant coated with highly crystalline hydroxyapatite. The coating is applied by plasma spraying. The problems associated with coating and implant surface with CPP via plasma spray coating are discussed on page 2, lines 1-10 of Appellants' specification. The plasma sprayed coating differs strongly in crystallinity and solution behavior from the mineral phase of bone.

The reference is silent regarding the particle size of HA or collagen. Thus, the reference does not teach hydroxyapatite crystals having a length of about 300 to 500 nm (i.e., 0.3 to 0.5 μm), in the presence of collagen. Additionally, JP 11-047259 is silent regarding a coated metallic implant with an outer layer of a bone analogous coating comprising a collagen matrix, which is constructed in layers. The implant coatings of JP 11-047259 are not constructed

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in the form of layers. Not only is the reference silent with respect to a least one layer of an implant coating comprising a composite of mineralized collagen fibrils, amorphous calcium phosphate, and crystalline hydroxyapatite, but the reference does not teach or suggest an electrochemically conducted coating process.

Constantz et al.

Constantz et al. teaches a hydroxyapatite coating for a prosthesis. The coatings of Constantz et al. may be combined with a wide variety of materials, such as collagen, bone growth factors, such as TGF-B, bone morphogenetic factor, combinations thereof or the like. These factors may be included in the reaction mixture or in a storage solution (see, for example, column 5, line 67 to column 6, line 6).

By combining JP 11-047259 and Constantz et al., a skilled worker would arrive at a substrate coated by a coating consisting of a simple mixture of hydroxyapatite (with extremely small amounts of amorphous calcium phosphate) and collagen. See line (c) in Figure 1 above. The combined teachings would not lead a skilled worker to an interconnected layered structure of a mineralized collagen matrix. This is especially true since Constantz et al. does not teach how to mineralize the collagen: The only teaching in Constantz with regards to collagen is: at column 5, line 67 to column 6, line 6 where it is stated that "These factors may be included in the reaction mixture or in a storage solution". The material produced by Constantz is precipitated by simple dipping of the substrate into a solution containing calcium, phosphate and other materials. There is no teaching or suggestion in Constantz to use cathodic polarization in the coating process.

Furthermore, there is nothing within Constantz to direct a skilled worker to choose a crystal size of 300 to 500 nm and since Constantz et al does not disclose any hint towards a mineralization of collagen, a skilled worker using hydroxyapatite crystals in the 10 nm to 20 000 nm size range would form a simple mixture of hydroxyapatite with other materials regardless of the crystal

size chosen. Thus, the claimed crystal size of 300 to 500 nm within a layered mineralized collagen matrix is obviously not derivable from Constantz et al. and/or JP '259, particularly since neither Constantz nor JP '259 use a cathodic polarization coating process.

Lussi et al.

Lussi et al. (US 5,167,961) teaches a process for the preparation of high purity natural bone mineral. Lussi starts with natural bone (ex vivo) matter, thus relating to a different technological field. The Lussi process is targeted towards better degreasing and "deproteination" of natural bone material. The thus obtained bone material can have a crystal size between 20 to 400 nm. Lussi does not teach hydroxyapatite crystals at all, much less crystals having a size of 300 to 500 nm. The natural and degreased bone material may be used as a remodeling implant or prosthetic bone replacement and may be absorbed on physiologically active substances. However, Lussi et al. does not teach or suggest how and in which form the natural bone material can be absorbed on a substance. The combined teachings of JP 11-047259, Constantz et al. and Lussi et al. would lead a skilled worker to an implant coated with crystalline hydroxyapatite and optional collagen by simply dipping in a solution.

Rhee et al.

The Examiner cites Rhee et al. (US 5,543,441) to support the idea that collagen in combination with mineral components implicitly tends to separate into layers. See, for example, column 3, line 66 to column 4 line 5. However, Rhee does not provide any physical characteristics of these layers. For example, Rhee is silent regarding at least one of the layers comprising a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite, wherein the crystals of the crystalline hydroxyapatite have a length of about 300 to 500 nm.

Furthermore, Rhee negatively characterizes these phases or layers, stating:

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"formulations containing reconstituted fibrillar atelopeptide collagen in combination with particulate mineral components (useful, e.g., for treating bone defects and fractures) exhibit physical instability with time, and tend to separate into several phases or layers. Further, the handling characteristics of such compositions are not ideal, and the malleability and elasticity of such formulations could be improved."

Thus, Rhee's characterization of the combination as instable, not ideal and needing improvement in malleability and elasticity, would lead a skilled worker away from attempting new ways of combining collagen and particulate minerals.

Additionally, Rhee uses calcium phosphate crystals right from the start. Rhee does not start with an electrolyte solution comprising calcium ions and phosphate ions. Rhee's simple mixture does not lead to a strong attachment of the crystals to the collagen fibrils, let alone to the specific crystal size of the present invention. Additionally, the solid formulation of Example 7 of Rhee et al. would not possess an electrochemical charge suitable for supporting an electrochemical migration and precipitation process.

Thus, neither JP '259, Constanz, Lussi et al. nor Rhee disclose or suggest a mineralized collagen matrix constructed in the form of layers, whereby at least one of the layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite, and wherein the crystals of the crystalline hydroxyapatite have a length of about 300 to 500 nm. The references are particularly silent regarding a metallic implant that is prepared by an electrochemically assisted process by means of cathodic polarization in an electrolyte solution comprising calcium ions and phosphate ions.

The rejection of the claims under 35 USC 103 is not supported by the record and should be reversed.

2) Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441) in further view Sauk et al (4,780,450).

The deficiencies of JP 11-047259, Constantz and Lussi are discussed above. Sauk et al. does not cure these deficiencies.

Like JP '259, Constantz and Lussi et al. discussed above, Sauk et al. doesn't teach an electrochemical process for coating an implant. Sauk et al. (US 4,780,450) relates to a porous composition comprising polycrystalline calcium phosphate ceramic, a phosphoryn calcium salt, and type I collagen for application in osseous repair. The composition is obtained by a simple mixing of the components. Sauk does not teach an electrolyte solution comprising calcium ions and phosphate ions. The composition taught by Sauk et al. would not give rise to a mineralized collagen matrix, with hydroxyapatite crystals formed directly on the collagen fibrils surface.

Furthermore, Sauk et al. does not teach or suggest a mineralized collagen matrix comprising mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length between about 300 to 500 nm.

Thus, the combined disclosures of JP 11-047259, Constantz et al., Lussi et al. and Sauk et al. fail to teach or suggest a mineralized collagen matrix as recited in Appellants' claims. The rejection of the claims under 35 USC §103 is not supported by the record and should be reversed.

3). Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by Rhee and in further view of Geistlich et al (5,573,771).

Geistlich et al does not cure the shortcomings of JP 11-047259, Constantz, Lussi and Rhee, which are discussed above.

Geistlich et al.

Geistlich et al. (US 5,573,771) teaches a purified particulate bone mineral

product, the particles of which may be coated or impregnated by a macromolecular material like, e.g., collagen or gelatin (cf. abstract and column 2, lines 11 to 33). To enhance the binding between the particles and the macromolecular material, the macromolecular material may be cross-linked. The thus obtained bone mineral product may be used as a remodeling implant, prosthetic bone replacement and for packing into a variety of bone cavities. Geistlich et al. doesn't mention the applicability of the bone mineral product for coating implants. As in the case of Lussi et al. discussed above, Geistlich et al. relates to a product which is made from natural organic (ex vivo) starting material, i.e., native bone product. Geistlich does not teach an electrolyte solution comprising calcium ions and phosphate ions. Thus, one skilled in the art that is confronted with the problem of manufacturing a synthetic implant coating for metallic implants would never have taken Geistlich et al. into account as being potentially relevant to solve his/her problem. Like Lussi et al., Geistlich et al. is non-analogous prior art. The present application is concerned with creating a bone analogous coating starting with an electrolyte solution comprising calcium ions and phosphate ions while Lussi and Geistlich already start with native bone material.

Furthermore, the teaching of coating or impregnating a material consisting of a bone mineral by a macromolecule (as derivable from Geistlich et al.) would not lead one skilled in the art to the present invention. Like JP '259, Constantz and Lussi et al, Geistlich are particularly silent regarding an electrochemical process for coating an implant. Thus, the disclosures of JP 11-047259, Constantz et al., Lussi et al. and Geistlich et al. fail to describe or suggest a mineralized collagen matrix as recited in Appellants' claims.

The rejection of the claims under 35 USC 103 is not supported by the record and should be reversed.

4) Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of

Lussi et al (5,167,961) as evidenced by Rhee and in further view of Liu (6,300,315).

The shortcomings of JP 11-047259, Constantz, Rhee and Lussi are discussed above.

Liu et al.

Liu et al. (US 6,300,3415) describes a strong, flexible collagen membrane and a method of making the same. The membrane is produced by precipitation of calcium phosphate mineral in a collagen slurry by maintaining a pH of at least 7.0. The precipitation of calcium phosphate mineral is induced immediately after mixing a 500 mM calcium ion containing solution and a 500 mM phosphate ion containing solution to the collagen slurry at a pH of about 9 (see Example 1 of Liu et al.). This results in the immediate precipitation of calcium phosphate resulting in a very loose network of calcium phosphate crystals and collagen fibrils.

Such an immediate precipitation of calcium phosphate does not promote the formation of calcium phosphate crystals directly on the collagen fibrils. Only a very loose network of calcium phosphate crystals and collagen fibrils is formed. The resulting collagen membrane cannot further be used in an electrochemical precipitation process since such a process requires charged particles and the collagen matrix according to Liu et al. no longer possess an electrical charge. Therefore, the migration and precipitation in an electrochemical process would be strongly hampered and would not provide a coated implant according to the invention. An electrochemical process requires imperatively charged particles. Only calcium ions and phosphate ions in their dissociated form possess charges.

Moreover, Liu does not disclose or suggest the use of hydroxyapatite crystals having a length of about 300 to 500 nm.

Thus, the disclosures of JP 11-047259, Constantz et al., Lussi et al. Rhee and Liu fail to describe or suggest Appellants' claimed invention. The rejection of the claims under 35 USC 103 is not supported by the record and should be reversed.

5) Claims 1, 3-5, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441).

The shortcomings of Liu, Lussi, and Rhee are discussed above.

Worch et al.

Worch et al. (US 6,524,718) does not cure the deficiencies of Liu, Lussi and Rhee. Worch describes a metallic object with a polyphase oxide coating having a metal oxide phase and at least one other organic and/or inorganic phase in an anodic polarization process. The organic phase can contain collagen and the inorganic phase calcium phosphate. An anodic polarization as described by Worch et al. promotes the formation of a metallic oxide phase on the implant surface followed by the incorporation of inorganic and/or organic component into the oxide phase such that polyphase oxide coating compares with an alloy (column 2, lines 55 - 59, Worch et al.).

Due to the anodic coating process the inorganic and/or organic phase are embedded or incorporated into the metal oxide phase of the implant. The inorganic phase does not form multiple layers on the implant surface. The anodic process of Worch does not enable the precipitation and formation of hydroxyapatite crystals on the collagen fibrils. An electrochemical precipitation combined with the formation of seed crystals on the fibrils as well as the implant coating occurs only in a cathodic polarization process. In the course of the cathodically conducted coating process according to the present invention, calcium phosphate crystals with a length of about 300 to 500 nm are formed and precipitated onto the collagen fibrils forming mineralized collagen fibrils that precipitate onto the implant surface.

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Also on page 19 of the February 2008 Office Action, the Examiner again asserts that, "the definition of adhered is to: To stick fast by or as if by suction or glue. To cause to adhere; make stick." The examiner points out that term "adhered to" does not exclude embedding since embedding is a way of joining (sticking or fusing) two surfaces together.

Appellants' respectfully disagree. "Adhere to said implant surface" is clearly distinguishable from "embedding" which according to Merriam Webster means "to make something an integral part of" (resulting in the surrounding mass being at all sides of the embedded material), while "adhering to a surface" inherently means "to fix onto a surface." Worch et al. explicitly discloses that an organic and/or inorganic component is to be incorporated into a metal oxide phase (column 2, line 55 to column 3, line 3). Into and onto do not have the same meaning.

One skilled in the art would find no teaching or suggestion in Worch of an implant coated with a mineralized collagen matrix comprising mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals with a length between about 300 to 500 nm. Additionally, as described above, neither Liu, Rhee nor Lussi et al disclose or suggest an implant content with a mineralized collagen matrix as recited in Appellants' claims. Thus, combining the teachings of Worch et al., Liu and/or Lussi et al. would not lead a person skilled in the art would to arrive at the implant of the present invention, particularly since all of the cited references are silent with respect to use of cathodic polarization in a coating process.

The rejection of the claims under 35 USC 103 is not supported by the record and should be reversed.

6) Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441) in further view of Sauk et al (4,780,450).

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The references Worch, Liu, Lussi, Rhee nor Sauk, discussed above, do not teach or suggest the present invention.

The anodic process of Worch does not enable the precipitation and formation of hydroxyapatite crystals on the collagen fibrils. Liu's process results in immediate precipitation of calcium phosphate. Such an immediate precipitation of calcium phosphate does not promote the formation of calcium phosphate crystals directly on the collagen fibrils. Lussi et al, starts with native degreased bone particles. Lussi does not teach hydroxyapatite crystals at all much less crystals having a size of 300 to 500 nm. One cannot simply substitute native bone particles, which already exist as clusters and, as such, would not attach themselves to the collagen fibrils.

Thus, combining the teachings of Worch et al., Liu and/or Lussi et al. would not lead a person skilled in the art to a matrix mineralized with collagen, particularly since all of the cited references are silent with respect to use of cathodic polarization in a coating process. The rejection of the claims under 35 USC 103 is not supported by the record and should be reversed.

7) Claims 1, 3-4, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441).

The deficiencies of Liu, Lussi and Rhee are discussed above.

Shirkanzadeh

Shirkanzadeh (US 5,205,921) describes an electrochemical method for coating a metallic implant with calcium phosphate, which may optionally be co-precipitated with collagen. The metallic implant might be used as a cathode. The

method described in Shirkanzadeh yields a coated implant that is structurally different from the present invention.

Shirkanzadeh's process yields a calcium phosphate coating layer having micropores or without pores entirely. Such a layer does not exhibit good biocompatibility or adaptability to the local surrounding tissue. A calcium phosphate layer does not resemble native bone material. As can be seen in Examples 1 and 2 (at Col. 4, lines 50- 67), the formed calcium phosphate layer is characterized by calcium phosphate crystal sizes of approximately 2 to 20 μm (2000 - 20,000 nm). The layer of Shirkanzadeh does not resemble native bone material (i.e., a bone analogous coating) and the size of the hydroxyapatite crystals are not between 300 to 500 nm, as in Appellants' claims.

As described above in the invention, the hydroxyapatite crystals grow on the collagen fibrils. The naturally given size of a collagen fibril is about 0,3 μm or 3000 Å (see, above mentioned, pp. 173 of Lehninger "Principles of Biochemistry"). Therefore, hydroxyapatite crystals formed on a fibril cannot be much larger than the size of a collagen fibril, i.e. about 300 nm. Thus, the hydroxyapatite crystals of Shirkanzadeh are far too large for the purpose of forming a mineralized collagen matrix. Applying hydroxyapatite crystals of a size much larger than collagen fibrils would lead to a domination of the mineral component and a simple admixture of the collagen into the mineral matrix and not a mineralized collagen matrix.

At page 20 of the February 2008 Office Action, the Examiner notes that Shirkanzadeh does not teach the combination of amorphous calcium phosphate and hydroxyapatite (1-IA) or the instant particle size of HA. For this, the Examiner relies on Liu et al. or Lussi et al. However, dispersed particles of calcium phosphate mineralized collagen, as taught by Liu, cannot be precipitated in the electrochemical process of Shirkanzadeh. An electrochemical precipitation process requires imperatively charged particles. A calcium phosphate mineralized collagen according to Liu does not possess an electrical charge anymore. Therefore, the migration and precipitation in an electrochemical process would be strongly hampered and would not provide a coated implant

according to the invention. As for the Examiners reliance on Lussi et al., as noted previously, Lussi et al. teaches purified native bone particles and further leads one away from choosing a hydroxyapatite particle size in accordance with the invention.

Combining the teaching of Shirkanzadeh with Lussi et al. would lead a person skilled in the art to a process where purified native bone particles having a size between 20 and 400 nm are added to the electrolyte solution of Shirkanzadeh containing calcium, phosphate and optionally collagen and a electrical current is applied. The native purified bone particles according to Lussi et al. already exist as clusters and, as such, would not attach themselves to the collagen fibrils. No crystal growth of calcium phosphate crystals on the collagen fibrils would take place and hence no mineralization process of the collagen fibrils would be started. At most such a process would give rise to an implant coating comprising calcium phosphate crystals with a size between 2 to 20 μm , purified native bone particles and optional collagen fibrils, which are only mixed into the mineral matrix.

Thus, even the combined teachings of Shirkanzadeh, Liu and Lussi et al would not lead one skilled in the art to an implant with the features of the claimed invention. In order to form bone analogous structures of interconnected layers, the calcium phosphate crystallite growth has to occur on and between the collagen fibrils. Shirkanzadeh only teaches a method for forming a single layer of hydroxyapatite on the surface of a metallic implant, Liu is silent regarding a metal surface of a metallic implant and Lussi et al., who uses purified native bone particles, teaches away from selecting the particle size of the instant invention. Shirkanzadeh, Liu and Lussi et al. are particularly silent regarding a multilayered coating whereby at least one layer comprises mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length of about 300 to 500 nm. Liu and Lussi et al. are particularly silent with respect to use of cathodic polarization in a coating process.

Rhee's teaching that collagen in combination with mineral components implicitly tends to separate into layers does not cure the deficiencies of

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Shirkanzadeh, Lui and Lussi. Furthermore, Rhee teaches that such layers are undesirable, thus leading a skilled worker away from trying to achieve a layered coating.

The rejection of the claims under 35 USC 103 is not supported by the record and should be reversed.

8) Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441) in further view of Geistlich et al (5,573,771).

The deficiencies of Shirkanzadeh, Liu, Lussi, Rhee, and Geistlich are discussed above.

As noted above, Shirkanzadeh does not teach the combination of amorphous calcium phosphate and hydroxyapatite (1-IA) or the instant particle size of HA. In order to form bone analogous structures of interconnected layers, the calcium phosphate crystallite growth has to occur on and between the collagen fibrils. The hydroxyapatite crystals of Shirkanzadeh are much too large for the purpose of forming a mineralized collagen matrix. Such large HA crystals would lead to a domination of the mineral component.

Liu is silent regarding a metal surface of a metallic implant and Liu's process results in immediate precipitation of calcium phosphate. Such an immediate precipitation of calcium phosphate does not promote the formation of calcium phosphate crystals directly on the collagen fibrils. Lussi et al, starts with native degreased bone particles. Lussi does not teach hydroxyapatite crystals at all much less crystals having a size of 300 to 500 nm. One cannot simply substitute native bone particles, which already exist as clusters and, as such, would not attach themselves to the collagen fibrils.

Shirkanzadeh, Liu and Lussi et al. are particularly silent regarding a multilayered coating whereby at least one layer comprises mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length

of about 300 to 500 nm. Liu and Lussi et al. are particularly silent with respect to use of cathodic polarization in a coating process.

Rhee, is relied upon for teaching that collagen in combination with mineral components implicitly tends to separate into layers. Rhee also teaches that such layers are undesirable, thus leading a skilled worker away from trying to achieve a layered coating.

The rejection of the claims under 35 USC 103 is not supported by the record and should be reversed.

9) Claims 6 and 26 are rejected under 35 U.S.C. §103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al. (5,167,961) in view of Sauk et al (4,780,450).

The shortcomings of Shirkanzadeh, Liu, Lussi, and Sauk are discussed above.

With regards to claim 26, none of the references of record teach a collagen matrix mineralized with a calcium phosphate phase. They are particularly silent regarding a calcium phosphate phase that is doped with fluoride, silver, magnesium or carbonate ions or combinations thereof and wherein the collagen is a mixture of collagen of types I to III.

The rejection of the claims under 35 USC 103 is not supported by the record and should be reversed.

10) Claims 1, 3-6, 8, 10, 12-16, 18-19, 23-25, 27-28 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Constantz et al (5,279,831) in view of Liu (6,300,315) optionally in further view of Lussi et al (5,167,961) and as evidenced by Rhee (US 5,543,441).

The material produced by Constantz is precipitated by simple dipping of the substrate into a solution containing calcium, phosphate and other materials. There is no teaching or suggestion in Constantz to use cathodic polarization in the coating process. As discussed above, the process of Constantz would lead a skilled worker to arrive at a substrate coated with a simple admixture of hydroxyapatite and collagen. See line (c) in Figure 1 above. Constantz et al. does not teach how to mineralize the collagen. In fact, the only teaching in Constantz with regards to collagen is at column 5, line 67 to column 6, line 6 where it is stated that "These factors may be included in the reaction mixture or in a storage solution".

Furthermore, there is nothing within Constantz to direct a skilled worker to choose a crystal size of 300 to 500 nm and since Constantz et al does not disclose any hint towards a mineralization of collagen, a skilled worker using hydroxyapatite crystals in the 10 nm to 20 000 nm size range would form a simple mixture of hydroxyapatite with other materials regardless of the crystal size chosen.

Liu is silent regarding a metal surface of a metallic implant and Lussi et al., who uses purified native bone particles, teaches away from selecting the HA particle size of the instant invention. Nor do Liu, Lussi or Constantz disclose a multilayered coating whereby at least one layer comprises mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length of about 300 to 500 nm. Liu, Lussi and Constantz are particularly silent with respect to use of cathodic polarization in a coating process.

Rhee, as noted above, teaches away from a layered implant.

Thus, the rejection of the claims under 35 USC 103 is not supported by the record and should be reversed.

11) Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Constantz et al (5,279,831) in view of Liu

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(6,300,315) optionally in view of Lussi et al (5,167,961) as evidenced by Rhee (US 5,543,441) in further view Sauk et al (4,780,450).

As discussed above, neither Constantz, Liu, Lussi, Rhee nor Sauk disclose a mineralized collagen matrix.

The material produced by Constantz is precipitated by simple dipping of the substrate into a solution containing calcium, phosphate and other materials. There is no teaching or suggestion in Constantz to use cathodic polarization in the coating process. As discussed above, the process of Constantz would lead a skilled worker to arrive at a substrate coated with a simple admixture of hydroxyapatite and collagen and not a mineralized matrix. Nor is there any teaching in Constantz et al. on how to mineralize the collagen. The only mention of collagen states: "These factors may be included in the reaction mixture or in a storage solution".

Liu and Lussi also do not teach how to mineralize collagen. Liu is silent regarding a metallic implant and Lussi et al., who uses purified native bone particles, teaches away from selecting the HA particle size of the instant invention. Constantz, Liu and Lussi are particularly silent regarding a multilayered coating whereby at least one layer comprises mineralized collagen fibrils, amorphous calcium phosphate and hydroxyapatite crystals having a length of about 300 to 500 nm. They are also silent with respect to use of cathodic polarization in a coating process.

Rhee, as noted above, teaches away from a layered implant.

The composition taught by Sauk et al. (US 4,780,450) also would not give rise to a mineralized collagen matrix, with hydroxyapatite crystals formed directly on the collagen fibrils surface. Nor does Sauk et al. teach an electrochemical process for coating an implant. Sauk et al. relates to a porous composition comprising polycrystalline calcium phosphate ceramic, a phosphoryn calcium salt and type I collagen for application in osseous repair. The composition is obtained

by a simple mixing of the components. Sauk does not teach an electrolyte solution comprising calcium ions and phosphate ions.

Thus, the combined teachings of the cited prior art, if taken together, would, at best, only lead a skilled worker to a simple mixture of collagen and calcium phosphate or hydroxyapatite, not to a mineralized collagen matrix as a coating for a metallic implant according to the invention. JP '259, Constanz, Lui, Lussi, Rheo, Sauk, Geistlich and Worch are silent with respect to use of cathodic polarization in the coating process and Shirkanzadeh does not teach the combination of amorphous calcium phosphate and hydroxyapatite (1-IA) or the instant particle size of HA. The hydroxyapatite crystals of Shirkanzadeh are much too large for the purpose of forming a mineralized collagen matrix. Such large HA crystals would lead to a domination of the mineral component.

As discussed above, a mineralized collagen matrix (according to the invention) has a structure that is bone analogous and thus, different from a simple mixture of calcium phosphate and collagen. The processes described in the prior art simply would not enable the precipitation and formation of hydroxyapatite crystals having a length of about 300 to 500 nm on the collagen fibrils.

Based on the above remarks is respectfully requested that the rejections under 35 USC §103 be reversed.

12) Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27-28 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-23 of U.S. Patent No. 6,524,718 (Worch et al.) in view of in view of Liu (6,300,315) in view of Lussi et al (5,167,961).

The claims of Worsch do not teach or suggest multiple layers on the implant surface. Furthermore, the anodic process of Worch's claims does not enable the precipitation and formation of hydroxyapatite crystals on the collagen

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fibrils.

An electrochemical precipitation combined with the formation of seed crystals on the fibrils as well as the implant coating occurs only in a cathodic polarization process. In the course of the cathodically conducted coating process calcium phosphate crystals with a length of about 300 to 500 nm are formed and precipitated onto the collagen fibrils forming mineralized collagen fibrils that precipitate onto the implant surface.

Liu et al. does not cure the deficiencies of Worsch since neither claim hydroxyapatite crystals having a length of about 300 to 500 nm.

The Lussi process starts with natural ground bone. The process is targeted towards better degreasing and "deproteination" of natural bone material. The claims of Lussi does not teach or suggest hydroxyapatite crystals at all and they are particularly silent regards HA crystals having a size of 300 to 500 nm.

Thus, the claims of Worsch, Liu and Lussi do not teach or suggest a mineralized collagen matrix that is constructed in the form of layers, whereby at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite, wherein the crystals of said crystalline hydroxyapatite have a length of about 300 to 500 nm. They are particularly silent regarding a metallic implant coated with a mineralized collagen matrix that is prepared by a cathodic process.

Based on the above remarks is respectfully requested that the obviousness-type double patenting rejection be reversed.

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The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

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(viii) Claims Appendix

1. (Previously presented) A coated metallic implant comprising a metallic implant having a surface and an outer layer, wherein the outer layer comprises a bone analogous coating comprising a collagen matrix mineralized with a calcium phosphate phase which is adhered to said implant surface, wherein the mineralized collagen matrix is constructed in the form of layers, whereby at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite, wherein the crystals of said crystalline hydroxyapatite have a length of about 300 to 500 nm and wherein said metallic implant is prepared by a process comprising:
 - a) coating a metallic implant material by immersion in a collagen solution at a pH of less than 8 and a temperature between 4 – 40°C, and
 - b) coating said metallic implant material with a calcium phosphate phase (CCP) in a electrochemically assisted process by means of cathodic polarization in an electrolyte solution comprising calcium ions and phosphate ions,wherein process steps a) and b) are performed simultaneously or sequentially.
3. (Previously presented) A coated metallic implant according to Claim 1, wherein the calcium phosphate phase of the matrix further contains octacalcium phosphate: $(Ca_8H_2(PO_4)_6 \cdot 5H_2O)$, brushite $(CaHPO_4 \cdot 2H_2O)$ or mixtures thereof.
4. (Previously presented) A coated metallic implant according to Claim 1, wherein the calcium phosphate phase is doped with fluoride, silver, magnesium or carbonate ions or combinations thereof.

5. (Previously presented) A coated metallic implant according to Claim 1, wherein the collagen is collagen of type I.
6. (Previously presented) A coated metallic implant according to Claim 1, wherein the collagen is a mixture of collagen of types I to III.
7. (Previously presented) A coated metallic implant according to Claim 1, wherein said coating further contains gelatin.
8. (Previously presented) A coated metallic implant according to Claim 1, further containing growth factors, peptide sequences, hormones, antibiotics or mixtures thereof.
10. (Previously presented) A coated metallic implant according to Claim 1, wherein the metallic implant is made of titanium or titanium alloy.
12. (Previously presented) A coated metallic implant according to Claim 1, wherein an additional process step b) is placed in front of process step a).
13. (Previously presented) A coated metallic implant according to Claim 1, wherein the process steps a) and b) proceed alternately a number of times.
14. (Previously presented) A coated metallic implant according to Claim 1, wherein the process steps a) and b) are combined into one step, the metallic implant material to be coated being electrochemically polarized cathodically in a collagen solution comprising calcium ions and phosphate ions.
15. (Previously presented) A coated metallic implant according to Claim 1, wherein a cathodic current flow of -0.2 to -50 mA/cm² flows for 25 to 40 minutes during the galvanostatic polarization in process step b).

16. (Previously presented) A coated metallic implant according to Claim 1, wherein the mineralised collagen matrix is layered.

17. (Previously presented) A coated metallic implant according to Claim 1, wherein the coating further comprises gelatin.

18. (Previously presented) A coated metallic implant according to Claim 1, wherein a cathodic current flow of -0.5 to -30 mA/cm^2 flows for 30 to 40 minutes during the galvanostatic polarization in process step b).

19. (Previously presented) A coated metallic implant according to Claim 1, wherein a cathodic current flow of -1 to -10 mA/cm^2 flows during the galvanostatic polarization in process step b).

21. (Previously presented) A coated metallic implant according to Claim 1, wherein the outer layer is 0.04-150 nm thick.

23. (Previously presented) A coated metallic implant according to Claim 1, wherein the metallic implant is made of titanium or titanium alloy.

24. (Previously presented) A coated metallic implant according to Claim 1, wherein the outer layer is 0.04-150 nm thick and said crystals have a diameter of 50-60 nm.

25. (Previously presented) A coated metallic implant according to Claim 24, wherein the metallic implant is made of titanium or titanium alloy.

26. (Previously presented) A coated metallic implant comprising a metallic implant and a coating made of a collagen matrix mineralized with a calcium phosphate phase

wherein the calcium phosphate phase is doped with fluoride, silver, magnesium or carbonate ions or combinations thereof and the collagen is a mixture of collagen of types I to III.

27. (Previously presented) A coated metallic implant according to Claim 1, wherein the coating is obtained by precipitating calcium phosphate from a solution in the presence of collagen.

28. (Previously presented) A coated metallic implant comprising a metallic implant having a surface and an outer layer, wherein the outer layer comprises a bone analogous coating comprising a collagen matrix mineralized with a calcium phosphate phase which is adhered to said implant surface, wherein the mineralized collagen matrix is constructed in the form of layers, whereby at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite, wherein the crystals of said crystalline hydroxyapatite have a length of about 300 to 500 nm.

(ix) EVIDENCE APPENDIX

None

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(x) RELATED PROCEEDINGS APPENDIX

None

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